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Clinical Dystrophia Myotonica first presenting as Gestational Diabetes

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Abstract

Myotonic dystrophy is a rare form of muscular dystrophy that is associated with glucose intolerance and hyperinsulinism, among other associated endocrinopathies.

It is a cause of infertility in males, and its effect on pregnancy of affected females has been described, generally a deterioration of their clinical symptoms, as well as other possible complications such as polyhydramnios, reduced fetal movement, preterm labour and postpartum hemorrhage; however, the occurrence of gestational diabetes (GDM) in myotonic patients has not been described in the literature, although it may account for some of the previously mentioned pregnancy related complications.

We present a 37 year old female who came to our attention with newly diagnosed GDM during her second pregnancy, and exhibited long standing physical signs of myotonia that worsened during her pregnancy.

Introduction

We present a woman presenting with gestational diabetes (GDM) who had features of myotonia worsened during her gestation and a family history suggestive of an autosomal dominant inheritance pattern of the disorder. A clinical diagnosis of Dystrophia Myotonica (DM) was made. We describe her clinical features, the pregnancy outcome and review the limited literature of this presentation as there are no previous descriptions of DM being first diagnosed due to GDM. Gestational diabetes (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, affects approximately 7% of all pregnancies with a variable prevalence depending on the criteria used for diagnosis as well as the ethnicity [1,2].

Increasing obesity, decreased physical activity and advanced maternal age are main factors that contribute to the observed increase in GDM prevalence [3].

Although the pathophysiology of gestational diabetes is well understood, attention must be given to any unusual symptoms that may indicate the presence of an underlying systemic disorder which may be causing the observed glucose intolerance in a pregnant subject.

Myotonic dystrophy is the most common neuromuscular disease in adults. It has a prevalence of 2.4-5.5 per 100,000 [4]. There are two clinical forms of myotonic dystrophy: DM1, also known as Steinert's disease, and DM2-proximal myotonic dystrophy. Both these conditions are autosomal dominant, and they share some clinical as well as genetic features [5].

Glucose intolerance has been described in both DM1 and DM2, among other endocrinopathies associated with these multisystem disorders [5].

Insulin resistance has been described in both DM1 and DM2, secondary to abnormal splicing of the insulin receptor in the skeletal muscles, rendering them less sensitive to insulin, hence the observed hyperinsulinaemia and the glucose intolerance among the affected patients [6].

Other possible mechanisms implicated in the pathophysiology of glucose intolerance among patients with DM may be increased plasma proinsulin concentration, as well as a higher than normal early secretory response following Oral Glucose Tolerance Test (OGTT) [7].

We hereby present a patient who was diagnosed with gestational diabetes during the second trimester of her pregnancy; however upon clinical evaluation she exhibited symptoms of myotonia and further investigations confirmed the diagnosis of DM.

Case presentation

Mrs. X is a 37 year old female patient, with a previous history of vaginal delivery in 2012, who presented to the combined diabetes- antenatal clinic with newly discovered gestational diabetes confirmed by a 75 gm 2 hour OGTT at 26 weeks of gestation (fasting glucose 4, 2 hour glucose following the administration of 75 gms of glucose = 7.8 mmol/L). The GTT was performed because of positive family history (father had T2DM).

Her first pregnancy in 2012 was unremarkable; her delivery took place at 40 weeks of gestation, giving birth to a healthy daughter with a birth weight of 3765 gms. She had

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forceps assisted vaginal delivery as labour had been slow to progress and she had a poor response to oxytocin. The infant was active and had no respiratory or feeding problems and continues to be well, achieving all her developmental milestones

During her regular Ante-natal outpatient review she mentioned that during this pregnancy she had been increasingly troubled with muscle stiffness, predominantly involving her legs, worse in the mornings and after prolonged sitting. This weakness and stiffness was gradually getting worse as the pregnancy was progressing. She did not recall any problems in her last pregnancy.

She recalled having some degree of muscle stiffness for most of her life, since the age of 10. During her adolescence she noticed some difficulty opening her eyes, and a lag that would usually follow following prolonged down gazing. Her symptoms would also get worse with cold, stress and in the morning. She denied any respiratory symptoms or any difficulty swallowing.

Although her symptoms existed for a long time, she never asked for medical attention before as they were mild and apart from some social embarrassment, considered to be clumsiness but they never interfered before with her daily activities.

Both her mother and maternal grandmother exhibited some symptoms suggestive of myotonia, and her grandmother spent the last few years of her life bound to a wheel chair; however they were never diagnosed with DM having not sought medical attention. On examination Mrs. X had wasting of her temporal muscles, and it was extremely difficult to release her fist. She also faced difficulty to stand up from sitting position. Myotonia was evident upon palmar percussion, and some stiffness was observed in her lower limbs as she was walking.

Her EMG showed frequent typical myotonic discharges in sampled muscles along with myopathic recruitment pattern. Nerve conduction studies were normal, excluding a neuropathic process. Her pelvic ultrasound showed an adequate for gestational age fetus, and no polyhydramnios.

Electrocardiogram and echocardiography showed normal heart tracing without any conduction defects or cardiomyopathy. Throughout her pregnancy she maintained adequate control of her gestational diabetes which was managed by dietary modifications as well as Metformin, 850 mgs twice daily. Her TSH was 1.8 and the rest of her investigations were unremarkable. She reported in each visit good fetal movements.

Genetic testing has not been straight forward with the usual genetic mutations involved with T1 or T2 DM not being found, however further genetic testing is still ongoing to look for new mutations and to rule out other forms of myotonia that are inherited in an autosomal dominant pattern. Mrs. X was induced at 39 weeks of gestation and she had a forceps aided uncomplicated delivery to a 3.4 kilogram healthy male fetus.

Her symptoms of myotonia improved following her delivery and she was quickly back to her baseline. Six weeks following her delivery she had a repeat of her OGTT which was normal [Table 1] and she was advised to maintain healthy lifestyle and follow up her blood sugar according to NICE guidelines through her GP.

Discussion

Myotonic dystrophy is a dominantly inherited muscular disease with an approximate estimated incidence of 1 in 8500 individuals [8].Two clinically and molecularly distinct forms of DM have been identified: DM1 and DM2.

DM1 (Steinert's disease) , is caused by the expansion of an unstable CTG trinucleotide repeat in the 3'untranslated region of the gene DMPK, which codes for a myotonin protein kinase expressed

in skeletal muscle. This trinucleotide (CTG) repeat is located on chromosome 19q13.3 [5,9].

CTG repeat lengths vary among individuals, but normally range from 5 to 37 in normal population. However clinically detected symptoms become apparent with counts exceeding 50 repeats (penetrance) [10].

The age of onset of the clinical syndrome is proportional to the number of the repeats, which in DM1 ranges from 50-4000 [5]. Patients with repeats of 50-100 usually have late onset, mild symptoms of the disease, and normal lifespan, whereas in individuals with repeats of 100- 1000 have early onset of their symptoms during childhood or early adolescence, with a more severe form of the disease and a reduced life span (48-60) [5].

Congenital DM is usually associated with repeats greater than 1000, and is characterized by infantile hypotonia, polyhydramnios, respiratory failure and cardio respiratory complications in their 3rd-4th decades [11].

CTG repeats greater than 37 are usually unstable; hence they are prone to expansion during meiosis and mitosis, leading to genetic anticipation [5]. Congenital DM almost always occurs following inheriting an expanded mutant DMPK allele from the mother [12].

DM2 is caused by a mutation in the ZNF 9 gene located on chromosome 3q21, due to expansion of the CCTG repeat in the first intron present in ZNF9 [13].

Both DM1 and DM2 are autosomal dominant, however the phenomenon of anticipation is less commonly described in DM2, and there is no congenital form of the disease in DM2 reported.

Both DM1 and DM2 are characterized by a constellation of symptoms with some minor differences between them. The classical musculoskeletal symptoms are progressive muscular weakness-distally in DM1 and proximally in DM2, characterized by sustained contraction (myotonia) [5].

Other forms of autosomal dominant myotonia have been described, as neuromyotonia, myotonia congenita and paramyotonia congenita; however there have been no reports of these conditions during pregnancy

The typical facial features include ptosis, weak eyelid closure, weak smile and thin facies, as well as frontal balding [11].

Cardiac manifestations include conduction defects tachyarrhythmias, as well as dilated cardiomyopathy [11].

Cardiac involvement is the main reason of the mortality among DM patients, and sudden death may occur in patients with severe forms of conduction defects [14].

Gastrointestinal symptoms usually involve dysphagia, constipation, pseudo-obstruction, and increased incidence of gallstones due to increased tone of the gall- bladder sphincter [15].

Posterior sub capsular cataracts; often described as "multicolored Christmas tree"; occur with increased incidence among those patients and usually present early during the fourth decade. Ophthalmoplegia has been described, but is not as common [11].

Age related cognitive decline may occur; [16] and some affected individuals may exhibit minor intellectual deficits or personality traits, such as passive -aggressive behavior and obsessive compulsive disorder [17]. Hypersomnia and hyperhidrosis have also been described [5].

Endocrine involvement usually occurs in the form of infertility due to the disappearance of the seminiferous tubules in males, menstrual irregularities in females, thyroid dysfunction, calcium dysregulation and hyperinsulinaemia [5,18].

Our patient had not had any problems in conceiving.

The increased production of insulin is thought to be a result of a relative insulin insensitivity which occurs due to an abnormal splicing of the insulin receptor to a less sensitive isoform in the skeletal muscles- isoform A. isoform A has a lower signalling capacity, and a twofold lower tyrosine kinase activity than it's counterpart,

Time from ingestion of glucose	Blood glucose
0 minutes	4.2
120 minutes	5.9

Table 1: 75 Gm Oral glucose tolerance test 6 weeks following delivery

isoform B, which is normally expressed in insulin sensitive tissues such as adipose tissue, liver and skeletal muscle [6].

Increased plasma proinsulin levels as well as a higher than normal early secretory response following OGTT has also been described in these patients [7].

DM has been described in pregnancy in literature, with most patients describing a worsening of their symptoms throughout the antenatal period, as our patient who we present described a rapid decline in her functional status as her pregnancy progressed [19].

Patients with DM have higher incidence of polyhydramnios; which is thought to be secondary to reduced fetal swallowing probably because up to 50% of the offspring are affected; spontaneous abortions, ectopic pregnancies, post-partum hemorrhage due to uterine atony, as also described in our patient's first delivery, placenta previa and preterm labor [4,19].

Increased maternal mortality due to serious anesthetic complications in patients undergoing caesarean section has also been described [20].

The occurrence of gestational diabetes, however has not been previously described in literature, although polyhydramnios is common, but this has been attributed to reduced fetal swallowing as discussed above [4,19,20]. Among the various reported cases, as well as some survey- based studies published describing different pregnancy-related complications in patients with DM, there has been no mention of evaluating these women for glucose intolerance during their pregnancies.

Khan et al. [20] described a 39 year old multiparous female with strong family history of DM, giving birth to a large (4,500 gm) baby, with associated mild polyhydramnios, however her glucose profile was not described in the report.

We would advise all patients with known Dystrophia Myotonica or if they harbor symptoms of myotonia to be assessed for gestational diabetes during pregnancy.

Conclusion

Pregnancy in patients with DM is a rarely reported entity that carries significant morbidity and mortality both to the mother and the fetus.

In light of the known association between DM and insulin insensitivity, pregnant patients with DM should be screened during their pregnancy to identify those with GDM and optimize their blood sugar control to minimize the risk of complications both to the mother and her fetus.

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